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Insulin: A 2014 Primer, Part 1

Editor's Note:

In this two-part insulin primer, the authors will explore all aspects of insulin therapy. The first article will review the currently available forms of insulin, their formulation, mechanisms of action, pharmacokinetics, and appropriate use in diabetes therapy. The authors will address the practical aspects of insulin therapy including when and how to start insulin, review titration regimens, and provide insight into selecting insulins to best match patient needs. In part 2, the authors will explore concentrated insulins and new insulins that may be available soon. They will also discuss insulin delivery methods and provide an introduction to insulin pump therapy for primary care physicians.

Introduction

Prior to the discovery of insulin, type 1 diabetes was a uniformly fatal disease. Treatment protocols called for patients to eat a very low carbohydrate diet to slow metabolic wasting that eventually lead to death. The development of pharmacologic insulin for routine use was made possible by the following significant accomplishments. In the late 1800s, Oskar Minkowski and Joseph von Mering discovered that animals with pancreatectomies developed severe cases of diabetes mellitus. The first use of exogenous insulin in a dog by Banting and Macloed resulted in the Nobel Prize in Physiology or Medicine.[1] In January 1922, they injected exogenous insulin in a 14-year-old boy who was dying at the Toronto General Hospital. After receiving the insulin he desperately needed, he improved and by the end of that month his glucosuria and ketonuria normalized.[1]

Initially bovine and porcine insulins were purified from animal pancreatic tissues and were used to treat people with diabetes. Since they were foreign to the human body, immune reactions were common, which resulted in an unpredictable treatment effect and duration. Ultimately, antibody formation

Executive Summary

The discovery of insulin provided a cure for a formerly universally fatal illness. With the development of multiple insulin formulations over the past several decades, the primary care physician benefits from a thorough understanding of these preparations and their utilization in modern diabetic care.

- Of the human insulins (regular, neutral protamine hegedorn, lente, and untralente), only regular and neutral protamine hegedorn are available today.
- The development of genetically engineered insulin includes three rapid-acting (aspart, lispro, glulisine) and two long-acting (glargine, detemir) analogs.
- Initiating insulin therapy usually means starting with a basal insulin with titration along with mealtime short-acting insulin modified by a "correction scale."
- Although insulin has one of the safest side effect profiles, it can lead to weight gain and hypoglycemia as well as the potential to further insulin resistance, particularly in type 2 diabetes.

was common and was a limitation to their use. In 1958, Frederick Sanger won a Nobel Prize in Chemistry for the discovery of the molecular structure of insulin.[1] Finally, Dorothy Hodgkin, who won a Nobel Prize in Chemistry in 1964, discovered the tertiary structure of insulin.[2] These discoveries allowed for the pharmacologic development of human insulin.

The development of human insulin was a significant advancement as it decreased immunogenic reactions and provided longer duration of action. Human insulin is produced by recombinant DNA technology, introducing the proinsulin gene into *Escherichia coli* or yeast. These organisms replicate and produce insulin. The production of insulin results in a dry powder.

Human insulins include regular (R) and neutral protamine hagedorn (NPH), lente (L), and ultralente (U). Only R and NPH are still available today. R insulin was used most commonly as mealtime insulin. Its kinetics are such that it should be dosed 30-45 minutes before a meal. This is a challenge for many people, as they cannot always predict the content and timing of food intake to that level of specificity. NPH insulin has a longer duration of action, can be dosed 4-6 hours before a meal, and is used 1 meal in advance (taken before breakfast to cover lunch) or as a basal insulin 2-3 times per day. NPH has a prolonged use due to the addition of a positively charged protamine. It is buffered with phosphate, which provides greater stability of the hexamers and slows the release as the active monomeric form. The stability of these insulins marked a great advancement in the treatment of diabetes, but they required a strictly regimented schedule with set eating times and specific carbohydrate intakes that were planned in advance.

The next step in the development of modern insulin came in 1980 when Sanger and Walter Gilbert shared a Nobel Prize in Chemistry for their contributions concerning the order of base sequences of insulin's nucleic acids.[1] By the late 20th century, after nearly 80 years of research, genetically engineered human insulin could now be manufactured in large quantities.

Meanwhile, the development of genetically engineered insulin analogs led to new formulations that made treatment even more convenient for people with diabetes. Today there are three rapid-acting analog insulins (Aspart, Lispro, Glulisine) and two long-acting analogs (Glargine, Detemir).

Biosynthesis of Insulin

Although sometimes debated, it is commonly agreed that the name "insulin" came from the Latin root for "islands" based on the microscopic appearance of the islands of Langerhans in the pancreas.[3]

Insulin is produced and released specifically by the ß cells of the pancreatic islet cells within the pancreas. Insulin is a polypeptide hormone that consists of two chains (chain A with 21 amino acid residues and chain B with 30 amino acid residues) linked by two disulfide bridges. The first form is preproinsulin. Soon after production, it is released from the rough endoplasmic reticulum when proteolytic enzymes cleave into pro-insulin. Then it is transplanted to the Golgi apparatus in microvesicles. Proinsulin converts to insulin when other proteolytic action cleaves the C chain (c-peptide) and leaves the active insulin molecule in the vesicle for secretion. This physiologic feature is convenient in that one molecule of c-peptide is produced for each insulin molecule. This makes c-peptide a good measure of endogenous insulin production, as it is not affected by exogenous insulin (whereas insulin levels would be affected).[4]

Insulin is active when it is in its monomeric form. The body can buffer insulin with zinc, which allows it to form dimers and hexamers that act as stabilizers to insulin, particularly in ß-cell vesicles. When insulin is injected into the subcutaneous tissue, it is usually in hexameric form and then dissociates into monomers. This rate of dissociation from hexamers and dimers is responsible for the onset and duration of action.

Normal Insulin Physiology[4]

Insulin secretion from the ß-cell vesicles is stimulated by a number of triggers. Glucose is taken up in the ß cell via a GLUT-2 receptor. When the glucose is not elevated, potassium ATP channels on the cell membrane allow potassium to leave the cell and keep the membrane at a negative action potential. When glucose levels rise above 90 mg/dL, glucose enters the cell and is oxidized by glucokinase (which also acts as a glucose sensor). When glucose exceeds these levels, the potassium ATP channel closes so potassium cannot leave the cell, leading to membrane depolarization of the ß cell, and thus causing voltage — gated calcium channels to open. Increasing intracellular calcium stimulates the release of insulin via exocytosis from the ß-cell.[5]

Human endogenous insulin secretion is continuous at baseline within the above parameters (basal insulin secretion). The pancreatic ß cell secretes insulin from vesicles in a pulsatile manner. The first pattern is a pulse every 6 minutes. The second pulse is every 30-40 minutes. The amplitude of these pulsatile secretions is based on the ambient glucose level presenting to the pancreas. There is a diurnal pattern as well whereby insulin secretion is lowest in the middle of the night and greatest first thing in the early morning. In a fasting state, insulin secretion suppresses glycogenolysis and stimulates gluconeogenesis and lipogenesis.

Insulin secretion is also modulated by the intake of nutrients (bolus secretion). In response to meal ingestion, insulin secretion is biphasic. There is a large and rapid first-phase insulin secretion followed by a slower and more sustained second-phase secretion. The incretin system significantly contributes to bolus insulin secretion via the gastrointestinal peptides (GLP-1 and GIP). These incretin hormones stimulate insulin release and suppress glucagon release from the pancreas. The incretin effect provides a much larger increase in insulin secretion than ambient glucose levels.

Insulin released from the pancreatic ß cell is then released into the portal venous system. The liver removes at least 50% of insulin released. The remainder is taken up into systemic circulation where it interacts with target site receptors. At the target sites, insulin binds to receptor sites on plasma membranes. This binding begins a cascade of intracellular reactions that trigger significant cellular responses such as glucose uptake, glycogen synthesis, and lipogenesis.[6]

Table 1: Pharmacologic Modification of Human Insulin to Change its Clinical Effect

Modification	Action	Insulin
Zinc buffer	Buffer to stabilize into dimer and hexamer	Regular NPH
Phosphate buffer	Buffer to stabilize into dimer and hexamer	NPH
Adding protamine (protaminate)	Allows for more stable association into dimers and hexamers	NPH Premixed insulins
Amino acid substitution	Allows for more rapid or slower dissociation of insulin into monomers	Apart Lispro Glulisine Glargine Detemir
pH change	Acidic insulin aggregates into hexamers	Glargine
Bind to FFA and albumin	Slows passive diffusion from subcutaneous to vascular to cellular space	Detemir

Pharmacologic Modification of Insulin

Table 1 includes ways that insulin can be modified to affect its pharmacokinetics and clinical effects.

Insulin Pharmacokinetics

The following discussion of insulin pharmacokinetics is organized according to duration of action, beginning with rapid-acting insulins and continuing through long-acting insulins. The insulins discussed are currently FDA approved in the United States for use in diabetes (*see Table 2*).

Rapid-Acting Insulins

There are three FDA-approved, rapid-acting insulin analogs available in the United States today: glulisine, lispro, and aspart. All three are clear, colorless solutions recommended for subcutaneous injection. They may be administered intravenously only when close medical supervision and monitoring are available. Timing of meals and monitoring for hypoglycemia are important with rapid-acting insulins.

Insulin lispro was approved in 1996 by Lilly with the brand name HumaLOG®. Lispro is a human analog insulin produced by a non-pathologic laboratory strain of *E. coli*. In this human analog insulin, the proline in position B28 is replaced by lysine and the lysine at position B29 is replaced by proline. Upon injection, insulin lispro is quickly absorbed, faster than regular injected human insulin. Lispro also has a shorter duration of action compared to regular insulin. Interchanging the amino acids allows for quick dissociation.

Table 2: Pharmacokinetic Profiles of Currently Available Insulins and Insulin Analogs

Insulin	Brand Name	Manufacturer	Species Source	Concentration	Time of Action (hours)		
					Onset	Peak Effect	Duration
Rapid							
Glulisine	Apidra	Sanofi-Aventis	human analog	U100	0.2-0.5	1.6-2.8	3-4
Lispro	HumaLOG	Lilly	human analog	U100	0.25-0.5	0.5-2.5	≤ 5
Aspart	NovoLOG	Novo Nordisk	human analog	U100	0.2-0.3	1-3	3-5
Short-Acting							
Regular	HumuLIN R NovoLIN R	Lilly Novo Nordisk	human	U100	0.5	2.5-5	4-12
Intermediate							
NPH	HumuLIN N NovoLIN N	Lilly Novo Nordisk	human	U100	1-2	4-12	14-24
Intermediate/Short-Acting Mixed							
70 NPH 30 regular	HumuLIN 70/30 NovoLIN 70/30	Lilly Novo Nordisk	human	U100	0.5	regular 0.8-2 NPH 6-10	18-24
Intermediate/Rapid-Acting Mixed							
50 lispro protamine 50 lispro	HumaLOG Mix 50/50	Lilly	human analog	U100	0.25-0.5	0.8-4.8	14-24
75 lispro protamine 25 lispro	HumaLOG Mix 75/25	Lilly	human analog	U100	0.25-0.5	1-6.5	14-24
70 aspart protamine 30 aspart	NovoLOG Mix 70/30	Novo Nordisk	human analog	U100	10-20 minutes	1-4	18-24
Long							
Detemir	Levemir	Novo Nordisk	human analog	U100	3-4	3-9	6-23
Glargine	Lantus	Sanofi-Aventis	human analog	U100	3-4	none	average 24
Miscellaneous Long							
Regular	HumuLIN R U500 (concentrated)	Lilly	human	U500	0.5	2.5-5	up to 24

Recommended time of administration for insulin lispro is 15 minutes prior to a meal.[7]

Insulin aspart (NovoLOG®) by Novo Nordisk was approved in 2000. This insulin analog is produced from recombinant DNA technology using saccharomyces cerevisiae (baker's yeast). The proline at position B28 is replaced by an aspartic acid. This interchange prevents the insulin molecule from aggregating, thus allowing for faster absorption. This insulin is recommended for subcutaneous administration approximately 5-10 minutes before a meal.[8]

Insulin glulisine (Aprida®) is a human insulin analog. Using a nonpathogenic strain of *E. coli*, asparagine at position B3 is replaced with lysine, and the lysine at position B29 is replaced with glutamic acid. Glulisine binds to insulin receptors on cell membranes. The change of amino acids seems to exhibit intracellular effects that speeds onset of action. This insulin can be given either prior to the meal or up to 20 minutes after the meal. Insulin glulisine was approved for use in 2004.[9]

Short-Acting Insulin

Regular insulin, which was FDA-approved in 1982, is a short-acting human insulin that is produced

using recombinant DNA techniques. Its form is a clear, soluble crystalline zinc solution. This insulin molecule will aggregate in dimers and hexamers when administered in high concentrations, which slows absorption. Regular insulin is normally administered 30-45 minutes prior to a meal and tends to last longer than rapid-acting insulins, anywhere from 4-12 hours. The duration of action is dose dependent. Regular insulin, which can be given subcutaneously or intravenously, is particularly useful as an intravenous infusion and is frequently used in hyperglycemic crises such as diabetic ketoacidosis and hyperglycemic hyperosmolar nonketosis syndrome.[10]

Intermediate-Acting Insulin[11]

Intermediate-acting insulin does not change the insulin molecule to illicit its effects. Neutral protamine hagedorn (NPH), or isophane, is a cloudy suspension that contains insulin and protamine. The addition of protamine creates a longer duration of action. When administered, enzymes slowly break down the protamine to allow for the slow absorption of insulin. NPH absorption is often variable, having an onset from 1-5 hours, and duration of action from 4-12 hours.[12] NPH insulin, which has been available since 1982, is available as HumuLIN N® (Lilly) or NovoLIN N® (Novo Nordisk). In the clinical setting, NPH is typically given one meal in advance or as 2-3 doses per day to serve as a basal insulin. The availability of long-acting insulins has led to decreased use of NPH insulin.

Premixed Insulins[10,12-14]

Developed to improve convenience for patients, premixed insulins are human insulin mixes and rapid analog insulin mixes. Human premixed insulin uses regular insulin and the premixed analog insulins use rapid-acting insulin analog so the time to onset, peak, and duration are dictated by the short-acting component. Patients should be instructed on the differences between these insulin mixes. Premixed insulins are named by the percentage of each component insulin/analog, with the longer-acting insulin being named first.

Human insulin regular and NPH can be mixed into a single syringe for administration. The two commercially available human insulin mixes are HumuLIN® 70/30 or NovoLIN N® 70/30 (70% NPH and 30% regular). The 70/30 mix is a cloudy suspension (as NPH is cloudy). The onset is around 30-45 minutes with a peak effect in 4-12 hours. This insulin is typically dosed 2-3 times per day with pre-breakfast and pre-dinner dosing. This is convenient for patients who want to limit the number of injections. Responses to this insulin, though, can be less reliable dose to dose. Regular insulin can precipitate out in the NPH insulin.

Other mixed insulins available include rapid-acting analog insulin and protamined rapid-acting analog insulin. The protaminated rapid-acting analog will delay absorption and give a prolonged effect. The HumaLOG® 75/25 and NovoLOG® 70/30 mixes have a more rapid onset of action and a shorter peak effect. This allows them to be dosed immediately before mealtime, which may result in more reliable clinical effects and reduced post-meal hypoglycemia. These rapid-acting mixed insulins came to market in the mid-to-late 1990s.

Long-Acting Analog Insulin

Insulin glargine (Lantus®) came on the market in 2000 followed by the release of insulin detemir (Levemir®) in 2005. The introduction of a steady, long-acting insulin closely mimics the basal rate of endogenous insulin. These agents alone have a lower risk of hypoglycemia due to the lack of a peak response and the continuous release of low levels of insulin.

Insulin glargine is a long-acting analog of human insulin. The insulin structure was modified by attaching two arginine amino acids to the terminal end of the B chain and changing asparagine to glycine at the terminal end of the A chain. These modifications produce a clear, colorless solution that is soluble in acid and forms a precipitate upon subcutaneous injection. This precipitate dissolves slowly, creating a continuous, steady release of insulin. Because of this mechanism, insulin glargine has no defined peak. Glargine is injected subcutaneously once daily and should not be administered intravenously or intramuscularly.[15] Given that glargine has an acidic pH, it should not be mixed with other insulins. Some patients report a burning sensation at the injection site as a result of the acidic pH, but this is not an indicator of any adverse effect.

Insulin detemir is a clear, colorless, long-acting human analog insulin. The threonine on the terminal end of the B chain is dropped and C-14 fatty acid chain is attached to the B29 lysine. When injected, the fatty acid chain reversibly binds detemir to albumin, which slows each step of absorption from the subcutaneous tissue to the cell. The onset of action is generally 1-2 hours. It can be given once daily. Insulin detemir is administered subcutaneously, but should not be administered intravenously or intramuscularly.[16]

Concentrated Insulin

Currently there is only one concentrated insulin clinically available in the United States (HumuLIN U500) but there are more emerging. These will be discussed further in the second part of this primer.

Cost of Insulins[17]

Insulin products range in price. The cash price for patients is approximately $26 per vial (10 ml or 1000 units) for Human insulin (R and NPH). A box of pens (generally 5 pens of 3 ml or 1500 units) of analog insulins can cost up to $350. Regular, NPH, and the mix of these are generally less expensive ($26 to $100 per vial). The newer,

more specific insulin products cost approximately $350 per box of pens. This does not account for insurance co-pays. Co-pays vary from plan to plan and coverage of specific brands also varies. Patients may require more than one vial or one box for a 1-month or 3-month supply. Often patients will have two different insulin products (for "basal/bolus" dosing) which means they will be paying for two insulin products. The prices listed above do not include the cost of needles, syringes, or other supplies, the added cost of which can play a significant role in patient adherence.

Table 3: Basal Insulin Algorithms

Measure	ADA/EASD	AACE/ACE	IDF	CDA
Algorithm				
Initial dosage	10 U/d	10 U/d	Not specified	10 U/d
Titration	2 U every 3 days	1-3 U every 2-3 days	2 U every 3 days	1 U every day
Target FBG, mg/dL	70-130	< 110[a]	<110	72-126
Target A1c, %	< 7.0	≤ 6.5	≤ 6.5	≤ 7.0

[a]Fasting blood glucose (FBG) target recommendation from the American Association of Clinical Endocrinologists (AACE) 2011 guidelines.

Abbreviations: ACE, American College of Endocrinology; ADA, American Diabetes Association; CDA, Canadian Diabetes Association; EASD, European Association for the Study of Diabetes; A1c, glycated hemoglobin; IDF, International Diabetes Federation.

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Practical Clinical Pointers for Insulin Use

When to start insulin? Insulin is the primary treatment for type 1 diabetes and eventually will be required by most people with type 2 diabetes. Current guidelines by the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (ACCE) support the use of insulin as early as 1 year after diagnosis if glucose remains uncontrolled after use of combination oral therapy and therapeutic lifestyle changes (ADA-European Association for the Study of Diabetes [EASD] and AACE guidelines). In addition, insulin may also be the preferred initial treatment for patients who present with severe hyperglycemia. This includes those with a fasting glucose > 250 mg/dL, A1c >10%, or acute symptoms of insulin deficiency including polyuria, polydipsia, and weight loss.

Some authors advocate for insulin as the first treatment for type 2 diabetes.[18,19] The underlying principle behind early intensive insulin use is that "resting" the pancreas in early diabetes may provide not only more rapid control of glucose but also a lasting or "legacy" effect on glucose control. While this is promising, this method of treatment requires further exploration.

How to start insulin? Primary care physicians treat the majority of patients with type 2 diabetes. Increasingly, insulin is part of the treatment plan for people with type 2 diabetes. For these patients, starting insulin usually means starting a basal insulin, glargine, detemir, or NPH. Basal insulins allow for suppression of hepatic glucose production overnight and can help normalize morning blood glucose. Therefore, controlling fasting glucose is a logical first step. By removing glucose toxicity, the remaining functioning ß cells are better able to address prandial hyperglycemia.

Basal insulin dosing depends on the current level of glucose control and which other medications are currently being used. The ADA/EASD recommend a starting dose of 0.1-0.2 units/kg as a single dose when the current A1c is 7-8% and 0.3-0.4 units/kg when the A1c is > 8%.[20] AACE has the same basal starting dose if the A1c is < 8% but recommends 0.2-0.3 units/kg if > 8%.[21] These starting doses are rarely enough insulin to normalize morning glucose at the first dose, so patients should be instructed to titrate the dose up by 2 units twice weekly until morning glucose reaches target range. Table 3 compares basal insulin titration recommendations from major diabetes organizations. A number of recommended insulin titration regimens have been studied, compared, and reviewed.[22]

Patient-driven titrations have proven to be more effective than physician-driven titrations.[23,24] When patients titrate their own insulin, it is recommended that physicians provide some parameters to limit or pause titration. Agreed upon stopping points include when the basal dose reaches 0.5 units/kg or when the patient experiences a hypoglycemic episode.[25]

To maximize adherence to therapy, the first injection should be taken in the office so the physician can teach the proper injection technique and allow the patient to demonstrate the correct technique. This practice also can help diffuse patient stress and diminish hesitancy before the first injection. Once patients have taken the first injection, they often comment how easy and painless it was. Further, by having the patient take the first injection in the office, the physician is communicating that this medication does not impair any ability to drive, as most patients drive home after leaving the doctor's office.

Which basal insulin should I start with? As mentioned earlier, there are two long-acting basal insulins and one intermediate-acting insulin that can serve as a basal insulin. All three formulations work well

Table 4: Factors Suggesting the Patient Is Getting Too Much Basal Insulin

Factors suggesting "overbasilization"
• More than 1 unit/kg daily of basal insulin
• Fasting glucose variability (wide range of first a.m. glucose readings without explanation)
• Hypoglycemia that occurs overnight or between meals
• Hypoglycemia that occurs if a meal is missed

to suppress hepatic glucose production. The analog insulins (glargine, detemir) have numerous benefits over NPH insulin,[26,27,28] including less hypoglycemia, especially nocturnal hypoglycemia; less weight gain; and less frequent dosing. The downside is the expense. Analog insulins are 3-5 times more expensive than generic human insulin. When dosing a basal insulin analog, it is recommended to start with a weight-based dose once daily. Many physicians have stayed with the initial recommendations to dose Glargine at bedtime, but dosing can, in fact, be any time of day based on the patient's schedule and preference.

There are a number of ways to titrate basal insulins. It is important to remember that when the dose is > 0.5 unit/kg, it is worth looking at post-meal glucose readings. It may be safer to add mealtime insulin than to continue to titrate basal insulin. Some people need large doses of basal and mealtime insulin. Many physicians will split very large doses of long-acting analog insulins (> 80 units/day) to allow for continued use of an insulin pen and reduction of depot effects from large single injections.

When NPH is used as a basal insulin, it is most commonly dosed 2-3 times per day. Twice-daily dosing, before breakfast and before dinner, is best. This minimizes hypoglycemia between meals and overnight. However, the time between dinner and breakfast the next morning may be longer than the duration of NPH insulin for some people. Under these circumstances, three times daily dosing of NPH is needed. It is important to note that adding three times daily dosing to a mealtime insulin will result in a very complex set of insulin actions and unpredictable hypoglycemia in a person who may not fully understand the dynamics of these insulins.

When is it appropriate to use premixed insulin? Premixed insulin combines a short-acting human insulin or a rapid-acting analog with an intermediate-acting insulin (NPH or protaminated rapid-acting analog). The premixed insulin is named by the percent long-acting insulin and then the percent short-acting insulin. For example, 20 units of Humulin 70/30 would be 70% or 14 units of NPH and 6 units of regular insulin. NovoLOG 70/30 would be 14 units of protaminated NovoLOG and 6 units of NovoLOG.

Premixed insulin allows a person to take fewer injections than a basal bolus regimen. However, it is more often associated with hypoglycemia and results in an inflexible daily and meal schedule to prevent hypoglycemic episodes.

Premixed insulin can be successfully used in people who have stable and reliable daily schedules with fixed meal times and fixed carbohydrate content. Premixed insulin can also be used for someone who has poor control but who is not motivated to engage in three or more shots per day. Premixed insulin may allow patients to achieve a more relaxed glucose goal and A1c target (≥ 8%).[30]

When to use meal time insulin? If a patient is able to achieve fasting glucose goals but the A1c is still elevated, or if the patient is still experiencing post-meal hyperglycemia, then attention should be shifted to address this defect. There are a number of options to treat postprandial hyperglycemia, including newer oral agents (DPP-4 inhibitors, SGLT-2 inhibitors), older agents such as the glinides or alpha-glucosidase inhibitors, and the shorter acting injectable GLP-1 receptor analogs.[31] The use of non-insulin injectables or oral agents is beyond the scope of this paper. Rapid-acting insulin analogs, which include aspart, lisine, and glulisine, can also be used.

Before starting mealtime insulin, it is important to make sure the patient is not getting too much basal insulin (overbasalized). If the basal insulin is covering some of the rise associated with mealtime ingestion, then the patient will be prone to more hypoglycemia once mealtime insulin is added.

The Endocrine Society, in cooperation with a number of other professional organizations, developed a decision tool for mealtime dosing. This reference (Accurate insulin decisions) is freely available for clinicians.[25]

How do I start mealtime insulin? There are two important questions to ask when starting mealtime insulin. How many meals do you plan to cover, and how do you plan to choose a dose? The goal of using mealtime insulin is to replicate physiologic insulin release. The patient takes an injection of mealtime insulin with each meal. The typical starting dose is 0.1 unit/kg per meal. If the patient has an elevated A1c > 8% or morning hyperglycemia > 160 mg/dL, then the dose of basal insulin can stay constant in addition to the mealtime dose. If the patient is well-controlled in the morning, the physician may need to subtract 10% of the basal dose to prevent hypoglycemia that could result from treating daytime hyperglycemia more effectively by using a mealtime dose of insulin. A patient who is getting a basal and bolus insulin regimen and who eats three

Table 5: Recommended Mealtime Insulin Titrations

Measure	ADA/ EASD	AACE/ ACE	IDF	CDA[a]
Algorithm Initial dosage	4 U	5 U	Not specified	Total daily dose of 0.3-0.5 U/kg; 40% of total = basal; 20% of total = bolus (3 times/d) 1 U every day
Titration	2 U every 3 days	2-3 U every 2-3 days	2 U every 3 days	NA
Target A1c level, mg/dL	< 7	≤ 6.5	≤ 6.5	≤ 7.0
Target A1c, %	< 180	≤ 140[b]	< 145	90-180[c]

[a]For initiation of intensive basal/bolus therapy.

[b]Postprandial glucose target recommendation from AACE 2011 guidelines.

[c]Adjust to 90-144 mg/dL if A1c targets are not being met.

Abbreviations: AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; ADA, American Diabetes Association; CDA, Canadian Diabetes Association; EASD, European Association for the Study of Diabetes; IDF, International Diabetes Federation; NA, not available; PPG, postprandial glucose.

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meals per day could take 4-5 injections per day. This is a significant task for most people and a necessity for those with type 1 diabetes, but it has come into question for type 2 diabetes.[32]

Make the dose of insulin match the food content. In type 1 diabetes, many patients are instructed to carbohydrate count in order to match the current dose of insulin to the food about to be ingested. This works well for people who are able to master this skill. Recently, however, some physicians are questioning whether this is beneficial for the majority of people with type 2 diabetes.[33] If a patient is not going to carbohydrate count, then the physician should either offer education on carbohydrate consistent diets or teach a more general dose adjustment in response to the size and carbohydrate content of a meal.

Recent studies support the principle of a basal plus 1 insulin schedule. In this scenario, the patient continues basal insulin, but only takes mealtime insulin with the largest meal of the day. For most people in the United States, this corresponds to the evening meal. When using a basal plus 1 regimen, the mealtime dose may be bigger at 0.1-0.2 units per kg.[32]

When should I use a correction scale? The term "sliding scale" has been replaced by "correction scale" to identify a different way to use insulin when current insulin needs are unknown. Correction scale insulin has historically been used in the hospital to limit times of prolonged hyperglycemia. When used alone or for prolonged periods of time, it has proven to be an ineffective treatment.

Correction scale insulin may be used alone for initial treatment if the person's insulin needs are unknown. However, it is intended that after 24 hours the "correction insulin" needed the previous day would be converted to scheduled insulin the next day that will prevent the need for ongoing "sliding scale insulin." Correction scale insulin is used in addition to scheduled mealtime insulin to supplement the current meal dose and correct a hyperglycemic reading in specific situations. Correction scales are more effective if the physician routinely reviews the need for correction. And, if needed regularly, this dose is then folded into the scheduled insulin dose.

Most correction scales can be individualized in people who are already on chronic insulin. To make a specific correction scale, the physician can use the rule of 1800 (the constant may vary from 1500-1900 based on the source). To estimate the amount of glucose reduction for 1 unit of insulin, take the total daily dose of all insulin injections and then divide this into the constant of 1800.[34]

Two examples are listed below.

Example 1. A person presents to the hospital with community-acquired pneumonia. He has no history of diabetes but he is hyperglycemic at the time of admission with a glucose of 212 mg/dL and no history of diabetes. Because this patient is acutely ill, sliding scale insulin is started using 2 units for every 50 mg/dL above 150 mg/dL. After the first 24 hours, he needs 20 units of insulin from the scale. Using the correction scale correctly, on day 2 the physician takes the total of the previous correction scale insulin from day 1 and converts it to scheduled insulin. Typically, half the insulin would be once-daily basal insulin (10 units) and the remaining scale insulin would be used to cover the meal content, divided equally among the meals (about 3 units per meal). This is repeated daily until the correction insulin need is negligible.

Example 2. A person with type 2 diabetes is on 40 units of Glargine each evening and 6 units of Lispro with each meal. She has been checking her glucose regularly and her fasting glucose is at goal. However, she is routinely high at lunch and dinner. She corrects for the high readings with an addition 4 units at these meals. To use correction

properly, the 8 additional units of insulin should be added to the scheduled mealtime dose. This can be divided to the 2 meals that she runs high and so 4 additional units will be taken at lunch and dinner to a total of 8 units to allow for better coverage of the meals.

Advantages and Disadvantages of Insulin Therapy

Insulin has one of the safest side effect profiles of any medication and has a very low rate of adverse effects or allergic reactions. Further, insulin is the most potent diabetes medication with the greatest ability to lower glucose levels and A1c. Insulin dosing can be quite specific and can be adjusted daily, if needed, for changes in background physiology. This makes insulin a nimble medication that can be adjusted to changes in the patient's daily and seasonal schedules.

The most common side effects of insulin are weight gain and hypoglycemia. These can be minimized by using some of the dosing suggestions from above. Some people may develop skin reactions to the injections but these can be significantly limited with proper injection education. Further, because insulin is given exogenously, the percentage that goes to the liver is less than with endogenous insulin. This may contribute to too great of a percentage going to peripheral tissues and thus furthering insulin resistance, particularly in type 2 diabetes.

Summary

Insulin is becoming an increasingly important component of diabetes treatment. With the pandemic of obesity and type 2 diabetes, rates of people needing insulin should climb dramatically. With new more physiologic insulins and advanced delivery methods, the use of insulin can be effective and convenient across a wide profile of patients.

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CME Questions

1. What is the best measure of endogenous insulin production?
   a. Serum insulin level
   b. Finger stick insulin level
   c. C-peptide
   d. Fasting insulin level
   e. HOMA-R (homeostasis modeling of insulin resistance)
2. Which of the following is a basal insulin?
   a. Glulisine
   b. Detemir
   c. Aspart
   d. Regular
   e. Lispro
3. Which of the following is a rapid meal time insulin analog?
   a. Lispro
   b. Detemir
   c. Glargine
   d. NPH
   e. Regular
4. In normal physiologic conditions, basal insulin production:
   a. is biphasic.
   b. is greatest around midnight.
   c. is stimulated by meal ingestion.
   d. is constant around the clock independent of other factors.
   e. matches hepatic glucose production.
5. When is a good time to stop basal insulin titration and look at mealtime glucose readings?
   a. When the A1c is above 10%
   b. When the person is taking 0.5 units/kg
   c. When the person is not willing to take insulin injections
   d. When the basal insulin is premixed insulin
   e. When the person reaches a fasting glucose routinely between 50 mg/dL and 70 mg/dL
6. Which of the following is true about basal insulin titrations?
   a. The post-dinner glucose is the best reading to use for titrations.
   b. Glucose readings are too variable to use for titrations.
   c. Patient-driven titration schedules work as well or better than physician office titrations.
   d. Titrations should occur no more often than 1 time weekly.
   e. Only physicians should direct insulin titrations.
7. Which of the following factors suggests that the person may be on too much basal insulin?
   a. He is taking more than 1 unit/kg per day.
   b. He has fasting glucose variability
   c. He experiences nocturnal hypoglycemia.
   d. He experiences hypoglycemia if he misses a meal
   e. All of the above

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